BEDSIDE MEDICINE FOR BEDSIDE DOCTORS

An Open Forum for brief discussions of the workaday problems of the bedside doctor. Suggestions of subjects for discussions invited.

VACCINATION

IMMUNOLOGIC PHASES OF VACCINATION

ANDREW J. THORNTON, M. D. (3235 Fourth Street, San Diego).—I like to think that every doctor has enough confidence in the immunizing properties of smallpox vaccination to recommend it to his patients, and with emphasis to advise them to have it done on both themselves and their children, not only once but repeatedly. Most of us back up this advice by performing vaccination on our patients whenever the opportunity is presented.

Each individual doctor has his own particular pet method of carrying out the process, but technique does not enter into the discussion here. Many of us have been doing vaccinations for so many years that possibly some of us have forgotten that the process is, in reality, highly technical and thoroughly scientific. I wonder how many of us give any thought to the various phases of immunity manifestations, and the different reactions that occur after vaccination in different individuals?

It has seemed, therefore, that a review of the subject of vaccination, with special emphasis on immunity and the significance of the various reactions, would be in order. I shall not at this time discuss the different methods of applying vaccination virus, but some reference will be made later on to the immunologic results of certain procedures.

Initial Vaccination.—The results of vaccination done for the first time on a patient are quite familiar to all, and need little discussion. The primary "take" runs a classical course. There is about three days' incubation period; three days' papular stage; three days' vesicular, and three days' pustular stages. These four stages succeed each other, in most cases, with marked regularity. The height of the course is reached about the twelfth day, and after that there follows a drying and crusting period, with a typical pitted scar when the scab drops off.

It should be assumed that any individual who has never been vaccinated, or who has not had smallpox, is susceptible to the disease and should respond to vaccination properly performed. If such a patient fails to get a "take," the reason for such failure is either an inactive virus, failure to insert the virus or some other fault in technique. We have all seen individuals who claim to have nursed smallpox patients, and have themselves never been vaccinated nor suffered the disease; but we cannot be influenced by such claims into exempting them from vaccination, especially in the presence of an epidemic.

The following statistics[1] will serve to lay emphasis. Of 321 persons who had never been vaccinated nor had smallpox, 98.4 per cent were successfully vaccinated on the first scratch. Of the five who did not get "takes," three responded on revaccination, making a total of 99.3 per cent.

Duration of Immunity. — Seven is a magical number which, I feel sure, has more significance in a certain game of chance than it has as an indicator of the duration of immunity from smallpox after vaccination. Jenner believed that a single successful vaccination conferred a lifelong immunity, and any failure in that regard was due to some improper technique in its application. However, the occurrence of smallpox in previously-vaccinated individuals became so frequent in the latter years of his life that vaccination itself was for a time seriously discredited.

Immunity wears off in time and each individual differs in that respect. Wilkins reports one case: a man of twenty years, who had been successfully vaccinated five times in sixteen years, and showed a good "take" which ran a course like a primary "take" on the sixth vaccination, although his last previous "take" was but one year old. Palmer and Rosenau report a medical student who had had four previous successful vaccinations, and then a primary "take" on their scratch.

On the other hand, we see many individuals who have had but one vaccination in forty years or longer. The following observations[1] will serve to illustrate. A total of 244 persons showed an average period of time, between two successful vaccinations, of 9.48 years. The results[2] of revaccination in 557 medical students showed the following: of 337 students vaccinated ten years or less previously, only one showed a primary "take." Of 168 students vaccinated ten to nineteen years before, there were six primary "takes." Fifty-two students vaccinated twenty years or longer showed only four primary "takes."

Thus we see that, after immunity is once established in the average person, primary "takes" are rarely found from subsequent vaccination even as long after as twenty years, and we are forced to the conclusion that in the great majority of cases immunity to vaccination lasts much longer than is commonly thought. In Germany the law formerly said: "The duration of immunity conferred by vaccination varies within wide limits, but averages about ten years." In England the Royal Commission on Vaccination said: "Vaccination protects during the years immediately succeeding the operation, probably from nine to ten

1 Wilkins: Ohio State M. J. (Jan.), 1927.

2 Dearing and Rosenau: Smallpox, J. A. M. A. (June 16), 1934.

years." Gillihan states that in the Orient it is said: On account of the extreme virulence of smallpox, vaccination is repeated at short intervals until the patient gives no further reaction to the virus.

Revaccination.—While the reaction after primary or initial vaccination is simple and easy of interpretation, that which follows revaccination is more complex and not so easily understood, unless one keeps in mind what the phases of reaction are and what each one means.

Recent studies on the subject have designated the reactions following revaccination as (1) immediate; (2) accelerated; (3) primary.

In the light of our present knowledge of allergy, the immediate reaction of revaccination is an allergic reaction. The individual has been sensitized to the virus, and reacts immediately. This indicates that his immunity has not worn off.

The accelerated reaction is also allergic, but is delayed; as compared with the immediate reaction, but accelerated as compared with the typical primary "take." This indicates that the immunity has partly worn off. The primary reaction is the classical "take" of the nonimmune person, and runs the usual course, as above described, and indicates immunity all worn off.

With these three distinct reactions in mind, we may discuss them more in detail. Immediate reactions were noted by Jenner, but were so slight and came so early in many cases that they were often overlooked. The immediate reaction comes within twenty-four to forty-eight hours usually, and is characterized by redness surrounding the site of the vaccination and develops a papule.

The California State Board of Health [3] declares that when an areola of 5 millimeters or more in diameter occurs, with or without papule at the site, within twenty-four hours after vaccination, then raises to maximum development within forty-eight hours and fades without forming a vesicle, the reaction is immediate.

If the areola reaches its maximum stage from the fourth to the seventh day and forms a small pustule which disappears more quickly than the lesion of an initial vaccination, then the reaction is accelerated.

Andervont and Rosenau,[4] experimenting with unheated vaccine virus and virus heated to 70 degrees centigrade for one hour in previously vaccinated persons, found that the heated virus produced a reaction with papules indistinguishable from the well-known immediate reaction. Also the reaction was as constant as was that of the unheated virus. The heated virus did not produce a reaction when used to vaccinate previously unvaccinated children, and did not produce immunity. Their studies further proved that the antigenic substance responsible for the immediate reaction was the virus.

Significance of Scar.—In examination of their data on immediate and accelerated reactions ten years or more after prior vaccination, Dearing and Rosenau found a distinct change during the period covered by their study. In the earlier years the percentage of immediate reactions was lower than in the later period. This change, they think, could be attributed to the difference in technique used in the two periods. Formerly, large insertions were made with the belief that the larger the scar the more prolonged the immunity would be. It is now known that a scar as small as one-eighth of an inch in diameter gives satisfactory immunity and a minimum of discomfort to the patient.

On the other hand, Gillihan [5] thinks that a scar one-half inch in diameter gives a more lasting immunity than a smaller scar. While Wilkins concludes that the amount of reaction of vaccination seems to depend upon (*a*) the size of the scratch; (*b*) the susceptibility of the patient, *i. e.*, the lack of immunity; (*c*) with the after-care taken. The average size of the scar from his vaccination, by actual measurements, was about 1.2 by 1.2 centimeters in diameter.

Conclusions.—Every attempt at vaccination should produce some reaction, and the formation of the vesicle is indirectly in proportion to the amount of immunity present in the patient.

Theoretically, therefore, the inoculator can read from the various reactions just the degree of immunity any individual has. It is well to remember, however, that immediate reactions were overlooked during the whole of the nineteenth century by everyone except Jenner and a few other outstanding students of the subject. The reaction is often so mild in degree that even medical students receiving instruction in the subject overlooked the papule until it either caused itching or was pointed out by the instructor.

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INTRADERMAL VACCINATION

OSCAR REISS, M. D. (312 Wilshire Medical Building, Los Angeles).—Ever since Jenner first described his simple scarification method of vaccination, attempts have been made to increase the efficiency of this highly effective measure of preventive medicine. The single scratch, the Pirquet chisel scarification, the multiple puncture, and various modifications of these methods, all have their firm adherents. Still another method, the intradermal, though less extensively used, seems to me to enjoy enough advantages to warrant rating it as the most desirable of all.

During the 1924-1925 Los Angeles epidemic of smallpox, it became necessary to admit smallpox cases to the Los Angeles General Hospital. This necessitated the vaccination of everyone associated with the hospital. After vaccinating a considerable number by the various cutaneous methods, with only a small percentage of "takes," it was decided to try the intradermal method, the use of which method had been advocated by Hoffman, Singer, Leiner, and Kundratitz in Europe, and by Wright, Twyman, Gettinger and Force in this country.

[3] Sawyer, Wilbur A.: Pub. Health Rep. (April 15), 1927.
[4] J. Immunol., 18:51 (Jan.), 1930.
[5] Am. J. Pub. Health, p. 906 (Sept.), 1927.

About 1,100 persons were vaccinated, and the following advantages were amply demonstrated:

1. *Exact dosage,* a known amount of virus can be introduced.

2. Certain absorption, because introduced intradermally.

3. Virus cannot be accidentally or purposely wiped off.

4. *Minimizes infection,* because there is no denuded skin surface.

5. No possibility of auto-inoculation.

6. *Requires no dressing.*

7. Resultant scar is much smaller.

8. Results in maximum percentage of "takes."

9. Immune reaction occurs if immunity exists.

10. Obvious advantages in persons with skin disease.

11. If no "take" or immune reaction, it submits evidence of dead virus or improper technique.

During the past ten years I have used this method exclusively, and in a series of 406 primary vaccinations have failed, in only nine cases, to secure a "take," and have not encountered a single instance of infection. When one considers how difficult it often is to convince parents of the need of having their children protected against smallpox in the first place, and how much more difficult it becomes to have the children returned for revaccination when the first attempt fails, the importance of using a method with 98 per cent success should be apparent.

A description of the technique, although frequently appearing in the literature, is worth repeating. A capillary tube of vaccine virus is broken at both ends, a tuberculin syringe with a short bevel, 27-gauge needle, is inserted, sucking out the contents of the tube into the syringe. One-tenth cubic centimeters sterile water is then drawn into the syringe. The skin over the brachial insertion of the deltoid is carefully cleaned with alcohol, and the contents of the syringe are injected intradermally at this site.

Usually, about the third or fourth day, a small macular lesion develops. However, the appearance of this lesion has in some instances been delayed as late as the twelfth day. The macular lesion then successively proceeds to vesiculation, pustulation, crusting and scaling, finally healing in from ten to twenty days with scar formation. The resultant scar in nearly all instances has been smaller and cosmetically less objectionable than what we had been obtaining by cutaneous methods.

It is important that the virus be introduced intracutaneously and not subcutaneously, because in the latter case a true skin picture of successful vaccination with the various stages above described may not appear, and visible evidence of a "take" will be lacking.

Usually on the sixth or seventh day, although sometimes as late as the fourteenth day, a constitutional reaction sets in, manifested by anorexia, malaise, and fever. The fever is usually slight, 99 to 101 degrees, but in some instances as high as 104 or 105 degrees Fahrenheit. In most cases it lasted only twenty-four hours. Only three children out of the entire group developed a badly swollen arm, with enlarged glands; but these signs all cleared up within seventy-two hours.

I am inclined to attribute the uneventfulness of this excellent clinical record largely to two factors: first, the method of vaccination used, and second, the fact that most of our group of children were vaccinated during the first year of life.

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CERTAIN COMPLICATIONS FOLLOWING SMALLPOX VACCINATION

CLAIN FANNING GELSTON, M. D. (Children's Hospital, San Francisco).—Klugh and King[1] give a most excellent résumé of *encephalitis* as a complication of vaccination: "The postvaccination cerebrospinal complication (encephalitis, encephalomyelitis, etc.), is a relatively newly recognized disease entity brought to the attention of the medical profession as recently as 1924. Of approximately seven hundred cases that have been recognized, only seventy-one have been recorded in the United States in the past ten years. By far the largest number of reports have come from Holland and England. Numerous cases have also been recorded in Germany, Sweden, and Norway. Occasionally, both in this and foreign countries, small, epidemic-like outbreaks have occurred, limiting themselves, however, to localized areas of population. The complications have occurred following the use of both rabbit-brain virus, guinea-pig virus, and strains of calf virus, obtained from various sources. The complications have followed both single and multiple insertion methods.

The specific causative agent of postvaccination cerebrospinal disease is not definitely known. Several theories have been advanced. Chief among these are:

1. That the vaccine virus itself is the causative agent.

2. That some unknown virus becomes activated by the vaccine virus, converting a latent encephalitis into an active one.

3. That the disease is a manifestation of an anaphylactic reaction, the vaccine virus acting as a sensitizing agent to nervous tissue.

Alternative theories advanced take into consideration vitamin or other dietary factor. Activation by vaccina of certain forms of bacteria, especially of the streptococci type, and of certain protozoa and yeasts, have also been suggested.

Eckstein[2] and his associates carried out clinical and animal experiments with a view to determining the course of vaccination, and any injury to the central nervous system caused by the vaccine, which could provide fresh points of view for forming an opinion on vaccination encephalitis.

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1 Klugh and King: Encephalitis as a Complication Following Vaccination, J. Arkansas M. Soc., Vol. 31, pp. 92-93, No. 6 (Nov.), 1934.

2 Eckstein, A.: Investigations on the Causes of Vaccination Encephalitis, Arch. Dis. Childhood, 7:105-116 (June), 1932.

They succeeded in proving that even in normal persons the vaccine virus could be demonstrated in the blood with great regularity. In these experiments they made use of the experiments of Othawara, who, after normal vaccination, could demonstrate the vaccine virus in the blood by its retention in the testicle of a rabbit.

"The blood of most of the patients was positive between the third and tenth day, especially between the sixth and eighth day after vaccination, also when the clinical manifestations were present."

"Although the view . . . that vaccination represents a local process accompanied by a secondary allergic reaction . . . was, considering certain abnormal vaccination reactions especially of general vaccines, not probable, and although the acquisition of a general immunity, following vaccination, was rather in favor of a general infection of the organism with vaccine virus, only experiments in a larger material of normal vaccinated children definitely proved this point. The occurrence of these general infections, especially affections of the central nervous system following vaccination, has a certain importance, as they find their analogues in numerous other infectious diseases."

This view was also confirmed by further observations that in no case of normal vaccination did the author succeed in proving vaccine virus in the cerebrospinal fluid; whereas in five cases of vaccinal injury of the central nervous system it could be demonstrated.

"There are two important points of view as to the causes of nervous complications following vaccination: (1) that the complications are due to an activation of the latent encephalitic germs caused by vaccination, or (2) that the vaccinations themselves are the cause of the complications."

The view gains ground that the vaccine virus itself is to be regarded as the actual cause of the complications. The author's clinical observations are in favor of this theory. In further experiments on monkeys, he was able to demonstrate that the presence of vaccine virus in the blood (also by directly injecting large quantities of the vaccine virus into the blood stream) did not give rise to any nervous affections as long as the barrier between blood and cerebrospinal fluid, as well as between blood and brain, is still intact.

"On the other hand, the presence of vaccine virus in the cerebrospinal fluid, also in very great dilutions, is connected with a meningo-myeloencephalitis running a typical course."

In other experiments, by producing different degrees of disturbance of the circulation of the central nervous system (unilateral ligature of the jugular vein), he also succeeded in exhibiting symptoms in monkeys which had a great clinical and morbid anatomical similarity to the so-called vaccination encephalitis observed in human beings. He obtained the same result by disturbing the current of cerebrospinal fluid by continuous lumbar punctures.

"As the experiments were carried out with a standardized (human) vaccine which was always previously tested as to its sterility, here only the vaccine virus comes into consideration as the injuring agent.

"When trying to form an opinion as to the case of vaccination encephalitis in human beings, attention was drawn over and over again to the fact that only in isolated cases has it been possible to prove vaccine virus in the brain of patients who died of vaccination encephalitis. But this proof loses its conclusive force in so far as the presence of vaccine virus in the blood is normal during the period in question, and therefore should, of course, not be looked upon as being pathogenic in the brain."

Postvaccination encephalitis tends to occur more in rural districts than in cities; girls are affected more often than boys. Infants under one year of age, though not immune, are seldom victims, as are also children over eight years of age. The larger proportion of cases have occurred following the primary "take" among children of school age, while adolescents and adults are practically exempt.

While the disease has occurred both following multiple and single insertions, most students of the subject regard the former as a greater predisposing method than the latter.

The nervous manifestations of postvaccination encephalitis are quite variable and may point to involvement of the meninges, the brain, the brain stem, the spinal cord or, as most frequently encountered, to a combined involvement of two or more of these structures. In spite of this variability of clinical symptoms, the disease as a distinct entity has been firmly established, mainly on the basis of the pathologic post-mortem findings, which are distinct and characteristic.

The incubation period is from four to seventeen days, most cases developing the first symptoms between the tenth and thirteenth days following vaccination. The uniformity of onset, course, and time relations of the symptoms in most cases is quite striking. The course of the disease is rapid, the fatal cases dying on the third or fourth day after onset of symptoms, or two weeks after vaccination. The earliest symptoms, as described by H. I. Viets and S. Warren, are: "Headache, vomiting, pyrexia, and a tendency toward paralysis. In infants convulsions, too, are frequent. Consciousness is soon lost. The paralysis consists of weakness of the cranial nerves or of the extremities, and there is considerable variation from time to time. The Babinski response is sometimes obtained. As the disease progresses the deep reflexes disappear. Sphincter control is usually disordered, incontinence being a common finding. Trismus has occurred in many cases."

The spinal fluid is clear, often increased in pressure, and no visible or cultivatable organisms can be demonstrated. The cell count is usually increased, containing mononuclear and polynuclear cells. In a few cases small amounts of vaccine virus were detected. On the other hand, frequently the spinal fluid is essentially negative.

In regard to the diagnosis, many cases have occasioned much confusion and have been mistaken for tetanus, epidemic meningitis, tuberculous meningitis, encephalitis lethargica, meningismus, poliomyelitis, cerebral hemorrhage, sunstroke, epilepsy, and hysteria. In differentiating, the history, the incubation period, course, and symptoms of the disease, as well as the spinal fluid and other laboratory findings are essential factors.

Very encouraging results, as are evidenced by recession of symptoms, abatement of the course, and hastening complete recovery, have been reported by foreign observers following the use of serum or citrated blood from individuals recently vaccinated or, preferably, vaccinated at the same time as the patient. The serum has been given both intrathecally and intravenously, most frequently by the latter route. Intravenously it has been given in doses from 8 to 10 cubic centimeters for one or two doses. In one case 5 cubic centimeters were given intrathecally, with striking results. Very good results have followed this treatment in severe cases even when used late, such as when the serum was given up to four days following onset of symptoms, or thirteen to sixteen days following the patient's vaccination. One case was benefited by the serum of the father, who had been vaccinated four years before.

The simplicity and accessibility of this method of treatment should serve to encourage its trial in every case.

Among the European cases the mortality rate is high, occurring in 50 per cent of the cases reported in England, and in 35 per cent of those in Holland. The mortality rate in this country has been estimated at 37 per cent. With rare exceptions, the nonfatal cases recover promptly and completely, leaving no sequelae. Exceptionally, residual symptoms persist, a case of marked mental deterioration and one of complete flaccid paralysis of both legs, with anesthesia below umbilical level, having been reported among the seventy-one cases of postvaccination encephalitis in this country.

There are several well-recognized factors in considering the prophylaxis of this dreaded postvaccination complication. Infancy may be considered as the best period to subject the individual to the primary vaccination, preferably during the first year of life. This should always be done with a suitable technique, one of which is defined by Charles Armstrong as "Employing a small superficial insertion, never over one-eighth inch in greatest diameter, and which employs no routine dressing." The same writer, on the basis of his experiments with mice, suggests that "inoculation with diphtheria toxoid tends to render these animals somewhat more resistant to vaccine virus subsequently administered intracerebrally. It is suggested that primary vaccination, especially after the first year of life, be deferred until contemplated immunization against diphtheria or other diseases by means of inanimate antigens has been accomplished."

Nervous children, or those with neurological ailments, should be excluded. In times when encephalitis, poliomyelitis or meningococcic meningitis are epidemic, vaccination should be postponed. Bed rest for three weeks, following vaccination, has also been suggested as a prophylactic measure.

In contrast to the lack of uniformity in the clinical symptoms of postvaccination encephalitis, the pathological picture, especially that referable to microscopic examinations, is constant, characteristic, and easily differentiated from that encountered in epidemic encephalitis (lethargic encephalitis) or in poliomyelitis of primary origin; on the other hand, the findings simulate closely those occurring in nervous system inflammations complicating such diseases as measles and scarlet fever.

Brookbank[3] reports a case which presented clinical and laboratory signs of *spinal meningomyelitis*. The sensory level seemed to indicate that the inflammation in the acute stage had progressed only to the level of the fifth dorsal segment, although motor signs pointed to mild inflammatory involvement in segments considerably higher. The sensory level two months after onset was in the eighth dorsal segment.

Cases of this type, with a definite sensory level in the spinal cord, are rare. Peake reported a case with the sensory level at the ninth dorsal segment in the acute stage, which cleared up almost completely within a month. Other similar cases have had either transient or no sensory involvement, the clinical picture simulating polio-encephalomyelitis. Spiller's cases were true smallpox.

Prodromal symptoms in the present case began on the thirteenth day after vaccination; in most reported cases onset has occurred between the tenth and thirteenth days. It has been noted that the disease is most severe between the ages of three and six years, and permanent sequelae give no approximation of their relative frequency; but mortality statistics indicate fatality in from 35 to 50 per cent of cases—the former figure in 150 Dutch cases in the period from 1924 to 1928; the latter figure in ninety-three English cases in the period from 1922 to 1928. In regard to other etiologic factors, it seems that there is no evidence of contagion and no seasonal variation, but twice as many cases have been reported in females.

Chalke[4] has made some interesting observations on *skin manifestations,* following vaccination. He states:

"Accidental vaccination lesions may appear either in the neighborhood of the original vaccination site, or in any other situation on the body, as a result of the introduction of the virus into a wound or abrasion. In this way a mother may be inoculated from the vaccinal pustule of her child, or the child may reinoculate itself. There is a greater tendency for this to occur when there is preëxisting skin disease, such as impetigo. Auto-intoxication is not, however, common and should not take place if proper precautions are taken to protect the vaccinated area. Lesions of accidental vaccinia may be distinguished from the focal rash of smallpox by their distribution and their number, but it must be remembered that the inoculation lesions not infrequently met with in smallpox are very similar in appearance. Patients, especially those who are smallpox contacts, displaying such pocks should be kept under observation for a few days, and carefully examined for the presence of a generalized smallpox rash. . . .

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[3] Brookbank, Thomas William: Postvaccinal Myelitis, J. A. M. A., 97:227-228 (July), 1931.

[4] Chalke, Hervert D.: Observations on Skin Eruptions Following Vaccination, Lancet, 220:578-581 (March 14), 1931.